Remarks

Entry of the present reply and reconsideration of this application is respectfully requested. Claims 28-43 are active in the application. Claims 28 and 37 are active and independent. Claims 16-18 and 21-23 are pending but withdrawn. Claims 1-15, 19, 20 and 24-27 are canceled without prejudice or disclaimer.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

In brief review, and as was stated in the remarks filed on December 18, 2009, concentrated and freeze-dried forms of methylcobalamin do not have a good long-term stability. As mentioned in the background section on specification page 2, JP S62-38, S63-3137 and H1-132514 disclose freeze-dried multi-vitamins preparations that included methylcobalamin but there were problems with these preparations including

- storage stability of freeze-dried preparations;

- a problem with the ability to re-dissolve the dried form in multivitamin preparations;

- photo-instability of concentrated methylcobalamin preparations; and

- a difficulty in guaranteeing the sterility of aqueous solution.

The invention embodies the discovery of a chemical environment in which freeze-dried methylcobalamin is stable. The inventors discovered that freeze-dried

compositions of methylcobalamin, including high concentration compositions, are very stable when the crystalline state of the excipient is suppressed, and specifically when stored freeze-dried with an excipient that comprises at least one sugar that is in an amorphous state, such sugar being selected from the group consisting of glucose, fructose, maltose, lactose, sucrose and trehalose, thereby arriving at the invention. Note that it is not required that the methylcobalamin itself be in the amorphous form, although it can be. Rather, it is sufficient if a sugar component of the excipient is in the amorphous form. The freeze-dried preparation of the invention that comprises methylcobalamin, and especially that comprises a high content of methylcobalamin, has excellent stability over time and can be used in high-concentration methylcobalamin therapy. As shown below, the combination of the cited art does not detract from the non-obviousness of the invention.

The Rejection under 35 U.S.C. § 103(a)

At Office action paragraph 5, claims 28-43 are rejected under 35 U.S.C. § 103(a) are being unpatentable over: Miyake *et al.,* (JP 63-313736; herein "Miyake") in view of Driskell, Sports Nutrition, CRC Press, page 75, (2000) (herein "Driskell"). The Examiner states that Miyake refers to Vitamin B_{12} as "cyanocobalamin" (at Miyake page 6, Table 1) but that it would be understood that vitamin B_{12} would necessarily comprise methylcobalamin also. Driskell (page 75) is relied on as teaching the active form of vitamin B_{12} is methylcobalamin. The Examiner states however, that even assuming

arguendo that the vitamin B_{12} disclosed by Miyake does not comprise methylcobalamin, the ordinary skilled artisan would have found it *prima facie* obvious to replace cyanocobalamin in the formulation taught by Miyake with methylcobalamin in view of Driskell.

Applicants respectfully traverse this rejection, and Examiner's comments thereon, and respectfully request reconsideration.

The Structures of Cyanocobalamin and Methylcobalamin Are Different

On a preliminary note, it should be clarified that the structures of cyanocobalamin and methylcobalamin are different. Cyanocobalamin has a cyano group at the position where methylcobalamin has a methyl group. Cyanocobalamin is not an active form and it is not made in nature. Cyanocobalamin must be converted into an active form. One of the active forms is methylcobalamin. Thus, the Examiner errs in concluding that by defining vitamin B_{12} as "cyanocobalamin" (at Miyake page 6, Table 1) that it would be understood that the vitamin B_{12} in the multipreparation comprised methylcobalamin also. On the contrary, by defining vitamin B_{12} as "cyanocobalamin," Applicants assert that the artisan would understand that Miyake's multivitamin preparation does not contain methylcobalamin.

Methylcobalamin is Not Photostable Even when Kept in a Brown Ampule and in the Presence of Mannitol

As shown below, at the time Applicants' priority application was filed, it was known that methylcobalamin, even when kept in solution in a brown ampule, with mannitol, is not photostable. There was no motivation to substitute the cyanocobalamin of Miyake with photo-unstable methylcobalamin.

As evidence of the photo-instability of methylcobalamin, enclosed for the Examiner's review is **Exhibit 1**, a copy of a form from the Japan Standard Commodity Classification system called an "Interview Form." The Interview Form contains details about commodities registered in the "Japan Standard Commodity Classification" system. Specifically, **Exhibit 1** is an Interview Form entitled

> "Therapeutic drug for peripheral neuropathy. Methycobal® Injection 500 μg (Mecobalamin drug product)."

Mecobalamin is another name for methylcobalamin. (*See* the chemical structure of "mecobalamin" on page 3 of **Exhibit 2.**)

An English language translation of the relevant portion of **Exhibit 1** is provided. The original Japanese language document is attached to the translation. The Interview Form is dated November 2000 and was prepared based on the package insert as revised in November, 1998.

The Examiner's attention is respectfully directed to Exhibit 1, English translation page 7, and the section beginning "Part IV. Drug product." Section 2 sets out that the composition of the drug product contains both 500 μg "mecobalamin" and 50 mg D-mannitol per ampule.

The Examiner's attention is then directed to section "3. Stability under different conditions," which is the last paragraph on page 7, and is copied below:

> 3. Stability under different conditions
>
> This product remains stable during storage under a usual fluorescent lamp as long as it is kept in the LPE pack (light-protect easy open pack). **However, it is subject to photodegradation while it is kept in the brown ampule without the pack.** Therefore, the product shall be protected from light and removed from the LPE pack immediately before use. (Emphasis added.)

Thus, Exhibit 1 establishes that mecobalamin (methylcobalamin) for injection, in the presence of D-mannitol, is subject to photodegradation, even when it is kept in a brown ampoule, unless it is protected from exposure to light.

At page 8 of the English-language translation of Exhibit 1, there is a chart at the top of the page and a graph at the bottom of the page. The graph at the bottom of page 8 shows data confirming the decomposition of methylcobalamin, upon exposure to light, to form hydroxocobalamin. After irradiating for only 120 min, the residue content of methylcobalamin was reduced to about 80%. This result demonstrates that methylcobalamin has a poor light resistance, that is, it has a low light stability. This is summarized in the chart at the top of page 8, right column, first box, in which it is stated:

> The drug product was degraded by light, resulting in reduced content and hydroxocobalamin production.

The data and information in Exhibit 1, establish that at the time the priority document was filed, methylcobalamin was known to be significantly photo-unstable. An

artisan who would consider substituting methylcobalamin for Miyake's cyanobalamin, has no motivation to substitute cyanobalamin with methylcobalamin, and no expectation of success in maintaining the stability of the methylcobalamin in Miyake's preparation simply by mixing it with an excipient, such as mannitol,.

The Photostability of Cyanocobalamin and Methylcobalamin is Different

The artisan who studied the photo-stability of cyanobalamin would have found that it was photostable as compared to methylcobalamin. As evidence that cyanobalamin is photostable, the Examiner's attention is respectfully directed to **Exhibit 3**, an "Interview Form" entitled "Vitamin B_{12} Preparation. Japanese Pharmacopoeia Cyanocobalamin Injection. <Nichi-Iko> 1mg." Exhibit 3 is an English language translation of the relevant portion. The original Japanese language document is attached to the translation.

In Exhibit 3, the Examiner's attention is respectfully directed to English translation page 3, which starts with "Part IV. Drug product," and, to section "4. Stability under different conditions," which is near the bottom of the page.

Within Exhibit 3, section 4, the Examiner's attention is further respectfully directed to subpart "(2) Photostability testing in ampule (light shielded ampule)." It can be seen that cyanocobalamin had a residual rate of 101.7% even after irradiating with a light intensity of 1.2 million Lux•hr.

The results presented in Exhibit 3 demonstrate that cyanocobalamin has a good light resistance. Therefore, if the artisan had performed experiments to evaluate the

photostability of cyanocobalamin under the conditions shown in Exhibit 3, the artisan would have found that it had a good photo-stability, in contrast to that of methylcobalamin.

Thus there was no motivation for the artisan to substitute methycobalamin in place of cyanocobalamin in the composition of Miyake.

Miyake in Combination with Driskell does not Lead to the Invention

Even if the skilled artisan did change the cyanocobalamin of Miyake to be methylcobalamin, the skilled artisan would not have arrived at the invention for at least two reasons:

(1) Miyake's preparation is a multivitamin preparation and addresses a problem unique to multivitamin preparations that contain polyoxyethylene cured castor oil and an excipient; and

(2) Neither Miyake nor Driskell suggest that the lyophilized preparation contain at least one sugar or sugar alcohol excipient that is in an amorphous state.

These points are discussed below.

Miyake is a multivitamin preparation

Miyake is directed to a problem that is unique to multivitamin preparations that contain at least one fat-soluble vitamin.

With multivitamin preparations, can be added as a surface active agent to assist in solubilizing the fat-soluble vitamins. Miyake's problem is that when solutions of a multivitamin containing a fat-soluble vitamin are lyophilized in the presence of a polyoxyethylene cured castor oil and an excipient, turbidity occurs when the freeze-dried preparation is redissolved. As a result, the art at the time of Miyake's taught that if polyoxyethylene cured castor oil derivative is used to solubilize the fat-soluble vitamins, no excipient should be added to the lyophylization.

To solve the problem of turbidity that appeared when polyoxyethylene cured castor oil derivative were used with an excipient in a multivitamin preparation lyophylization, Miyake added a polyhydric alcohol to the preparation. See claim 1 (on page 1) in this regard. Claim 1 is directed to a multivitamin freeze-dried preparation containing a polyoxyethylene cured castor oil derivative, an excipient and polyhydric alcohol.

See also Miyake Table 1 on page 8, and the Examples. The required polyhydric alcohol is exemplified by glycerol and propylene glycol in the Examples.

Miyake mentions mannitol and "other sugar alcohols, lactose, maltose, and other monosaccharides, oligosaccharides. . ." on page 6 (first full paragraph), evidentially for use as excipients as, in the last line on page 8, Miyake states that lactose was added as an excipient to the exemplified compositions. The presence of an excipient in the examples was necessary to create the turbidity problem that occurs upon redissolving multivitamin freeze-dried preparation containing a polyoxyethylene cured castor oil derivative

(Control Example 1 "CE 1"). However, it was not necessary that any part of the excipient be in an amorphous state.

In fact, Miyake teaches that Miyake's problem that is caused by the presence of the combination of an excipient and a polyoxyethylene cured castor oil derivative in the lyophilized preparation can be solved by either (1) eliminating the excipient (Miyake's background art) or by (2) adding a polyhydric alcohol to the preparation. Both of those solutions lead away from the invention as the invention not only utilizes an excipient but also the composition of the invention does not require a polyhydric alcohol.

Miyake only adds the excipient, such as mannitol, to compensate for the presence of a surface active agent, and the surface active agent in Miyake is only desired because of the fat soluble vitamins that are present. If there are no fat soluble vitamins, then the surface active agent is not needed, and, under Miyake's disclosure, neither would the excipient be needed. Thus the Examiner errs in concluding that Miyake renders obvious the claimed invention in which purified preparations of methylcobalamin can be stabilized, using an exipient that is at least partially in a specific chemical state, the amorphous state. The Examiner's hypothetical modification of Miyake to replace cyanocobalamin with methylcobalamin disclosed by Driskell would still not arrive at the invention even if all the other vitamins in Miyake's composition were removed. Moreover such a change would fundamentally alter the principle of operation of the preparation of Miyake.

Driskell does not cure the deficiencies of Miyake. There is no reasoned basis or motivation for the ordinary skilled artisan to rely on Driskell as a suggestion to replace

cyanocobalamin in the formulation taught by Miyake with photo-unstable methylcobalamin.

Miyake's Lyophylization Does Not Require Production of an Amorphous State

Further, Miyake, even in combination with Driskell, does not arrive at the invention because neither document teaches or suggests that the excipient comprise at least one sugar that is present in an amorphous state, or, at least one sugar alcohol be present in an amorphous state.

Miyake mentions "mannitol and other sugar alcohols, lactose, maltose and other monosaccharides, oligosaccharides" and "dextran" on page 6, last full paragraph. However, even if Miyake utilized a saccharide or sugar alcohol in the preparation during the lyophylization, there is no evidence that Miyake lyophilizes under conditions in which, after lyophylization, at least one sugar or sugar alcohol is in an amorphous state.

It should be recalled that previously cited art, Makino *et al.*, US 4,984,788 and Kim *et al., J. Pharm. Sci. 87*:931-935 (1998) establish that mannitol can be present in crystalline and/or amorphous forms depending on the conditions during the freeze drying procedure (*see,* for example, the discussion at the bottom of page 16 in the amendment and reply filed December 18, 2009). Miyake's disclosure does not specify the freeze drying process condition, much less lead the artisan to a conclusion that the condition must be such that a sugar or sugar alcohol must be present in the amorphous form in the lyophilized preparation. This deficiency is not cured by Driskell.

Thus, even assuming *arguendo* that the vitamin B_{12} disclosed by Miyake does not comprise methylcobalamin, the ordinary skilled artisan would not have found it *prima facie* obvious to replace cyanocobalamin in the formulation taught by Miyake with methylcobalamin in view of Driskell, and to lyophilize the same so as to provide a preparation suitable for the long term storage of methylcobalamin with at least one sugar or sugar alcohol that is present in an amorphous state.

The evidence above establishes that the invention, even if characterized as a combination of familiar elements, yields more than predictable results. That is, the invention/improvement is more than the predictable use of the prior elements according to their established functions. The invention is more than a simply substitution of one known element for another to obtain a predictable result. Thus, the invention is non-obvious.

Moreover, the discussion above has shown that the rational underpinning of Examiner's articulated reasoning does not support a legal conclusion of obviousness. The combination of the cited art is silent a method to increase the long term stability of freeze-dried methylcobalamin preparations, and especially, high-content methylcobalamin preparations, and compositions with such stability. Miyake is concerned with a different problem, and, also, Miyake teaches away from the invention. Driskell does not cure any of these deficiencies.

However, even if such a suggestion is found, Applicants have provided evidence that the combination of Miyake and Driskell does not create a reasonable expectation of success in arriving at the invention. Accordingly, Applicants respectfully assert that

prima facie obviousness is not established, or, if it has been established, it has been overcome.

Conclusion

Prompt and favorable consideration of this Reply is respectfully requested. All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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